REMARKS

I. Status of The Claims

Claims 45-67, 69, 81-87 and 89 are under examination. Claims 68, 70-76 and 88 are cancelled. Applicants cancel claims 48, 49, 57, 58, and 89 without disclaimer or surrender of the subject matter recited therein. Claims 77-80 are withdrawn. Applicants have amended claims 45, 46, and 50 by deleting "modifies the rate of joining" and inserting "activity that joins." Applicants have also deleted "wherein said electrode is not a carbon electrode" from claims 55, 56, and 60.

Applicants have also amended claim 60 by deleting "capture moiety" and inserting "solid phase, wherein said solid phase is not a graphitic nanotube." Support for this amendment can be found in the specification, including page 11, line 28 to page 12, line 3 and page 14, lines 5-7. Applicants have also amended claim 60 by deleting "capturing" and inserting "immobilizing" to parallel the language of the other claims.

New claims 90-94 are provided. These claims correspond to claims 48, 49, 58 and 59 which were cancelled and written in independent form. Support for new claims 90 and 91 includes pending claim 46, while support for new claims 92 and 93 includes claim 56. Additional support for the new claims can be found in the specification on page 13, line 24, to page 15, line 5, and page 14, line 22 to page 15, line 5.

New claim 95 is also provided. Support for new claim 95 includes page 12, lines 9-14. No new matter has been added by any of the amendments.

II. Interview

Applicants thank the Examiner for the interview held at the U.S. Patent and Trademark Office on April 11, 2007. Applicants have amended the claims in accordance with the Examiner's helpful suggestions. Applicants discussed the rejections of record with the Examiner, and came to agreement. This response reflects the substance of the interview.

III. The Claimed Methods are Not Obvious

The Office previously rejected claims 45-67, 69, 81-87 and 89 as under 35 U.S.C. § 103(a) allegedly obvious over Shukla *et al.*, 22(9) Nucleic Acids Res. 1626-31 ("Shukla") in view of Massey *et al.*, U.S. Patent No. 5,866,434 ("Massey"). Office Action, September 15, 2006, p. 2. The Office maintains this rejection in the current Office Action. Office Action, January 12, 2007.

Applicants respectfully traverse. Neither Shukla, Massey nor the combination of the two establish *prima facie* obviousness. *Prima facie* obviousness requires that three criteria be met:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2142.

None of these three requirements are satisfied by Shukla, Massey or their combination. Because the enzymatic step which occurs differs between the pending claims (joining vs. cleaving), Applicants address the rejection of the "joining" claims and

the "cleaving" claims separately. Where a dependent claim depends from both groups, Applicants' those claims are included in both sections.

IV. Claims That Recite Enzymes That Join Substrates

Claims 45-54, 65, 67-69, and 81-87 recite methods for assaying a sample for an enzyme that modifies the rate of joining substrates. Applicants have amended claims 45, 46, and 50 by deleting "modifies the rate of joining" and inserting "activity that joins," merely to simplify the claim language at the Examiner's suggestion. Shukla, Massey or their combination, fail to render these claims obvious because they do not disclose all the elements of these claims, they fail to provide motivation to combine, and an expectation of success.

A. Shukla, Massey or their Combination Fail to Teach all the Limitations of the Amended Claims

The Office rejects claims 45-67, 69, 81-87 and 89 over Shukla stating that Shukla does "teach assaying an enzyme that modifies the rate of joining of two substrates." Office Action, of September 15, 2006, p. 2. The Office asserts that "the term modifies does not necessarily read on joining two substrates rather it reads on changing or modifying the rate of joining." Office Action of January 12, 2007, p. 2.

Applicants have cancelled claim 89 rendering the rejection of this claim moot. Applicants' amendment of claims 45, 46, and 50 eliminates the word "modifies," and the amended claims now recite "an enzyme activity that joins a first substrate with a second substrate." Shukla does not teach or suggest any method for measuring the activity of an enzyme that joins substrates, much less the specific claimed measuring method, but teaches an assay for a DNA helicase, and enzyme which separates a substrate into

products. *See* Shukla, Figure 1. Accordingly, the amended claims are not obvious in view of Shukla.

Massey does not cure the deficiencies of Shukla, because Massey also fails to teach or suggest any method for measuring the activity of an enzyme that joins substrates to form a product, much less the specifically claimed method. The Office states that Massey "teach[es] a method of claims 45-46, 50, of assaying a sample for an activity that modifies the rate of joining that joins (binds) a first substrate (an assay-performance substance) and a second substance (a functionalized graphic nanotube) to form a product (binding complex) ...." Office Action, September 15, 2006, page 4.

Applicants respectfully disagree with the Office's previously asserted understanding of the binding reactions in Massey. Massey describes the direct binding of an analyte of interest to a "functionalized, graphitic nanotube." It does not describe or suggest using this assay to measure an enzyme activity that joins two enzyme substrates to form a product. Applicants assert that "binding" as contemplated in Massey is not equivalent to the enzymatic joining of two enzyme substrates described in the instant application. In a binding assay, there are two substances that interact, but not a third substance, such as an enzyme, which influences the rate at which the two substances join. Figure 4 of Massey is a representation of the binding of a DNA probe to a complementary DNA. No enzyme is involved in this binding reaction, and thus it is not an enzymatically-catalyzed joining reaction as recited in the pending claims.

In sum, combining Shukla with Massey fails to render the claimed methods obvious because these publications do not teach or suggest any method for assaying a

sample for an enzyme that joins substrates to form a product, and certainly do not teach the specific method claimed.

B. There is no Motivation to Combine Shukla and Massey and No Expectation of Success

The Office asserts that the skilled artisan

> "would be motivated to combine the method as taught by Shukla *et al.* with the chemiluminescent label detection as taught by Massey *et al.* because Massey *et al.* explicitly taught the use of luminescence assays using particles having high surface area for immobilization of assay performance substances to achieve advantageously high light emission."

Office Action, September 15, 2007, p. 6. According to the Office it would be obvious to combine Shukla and Massey "for the propose of enhancing the efficiency of detecting the enzyme activity in that sample." *Id.*

Applicants respectfully traverse. As noted above, Shukla and Massey fail to teach or suggest any method for assaying a sample for an enzyme that joins substrates. Accordingly, one of skill in the art wishing to use a method for assaying a sample for an enzyme that joins substrates would have not motivation to combine two methods that neither teach nor suggest assays for measuring enzymes that join substrates. As such, one would have no expectation of success in arriving at the claimed methods.

In view of the forgoing, Applicants respectfully request that the Office withdraw the rejection of claims 45-67, 69, and 81-87.

V. Claims Which Measure Enzymes that Cleave Substrates

Shukla and Massey, and the combination of the two fail to render claims 55-64, 67, 69, and 85-87 obvious because they do not disclose all the elements of these claims, and they fail to provide motivation to combine and an expectation of success.

A. Shukla, Massey or Their Combination Fail to Teach All of the Limitations of the Claims

According to the Office it would be obvious to the skilled artisan to combine Shukla with Massey "for the purpose of enhancing the efficiency of detecting the enzyme activity in said sample" Office Action, September 15, 2006, page 6.

1. Claims 55 and 56

Applicants respectfully traverse. Shukla assayed for hydrolytic enzymes by detecting radioactively labeled products of the enzymes. Shukla, p. 1627, col. 2. Shukla does not teach or suggest the use of ECL in the methods disclosed. Moreover, neither Shukla nor Massey describe how a product bearing an ECL label could be used in the method of Shukla. In Shukla, the product of the reaction is blotted to a membrane. Shukla, Figure 1. Nothing in Shukla or Massey discloses how an ECL-labeled product, that is bound to a membrane, could be brought in close proximity to an electrode for measurement of light produced by the ECL label. Moreover, each of claims 55 and 56 recite that the "luminescent label is linked to said substrate and said substrate is linked to said electrode." Shukla does not teach or suggest a substrate that is linked to both a luminescent label and an electrode. Accordingly, Shukla does not render claims 55 and 56 obvious.

Massey does not cure the deficiencies of Shukla. Massey teaches the use of a graphitic nanotube which is bound to a enzyme substrate. Figure 3 of Massey describes such an assay substrate. An assay using such a substrate is described in column 14, lines 21-36. In this assay, a graphitic nanotube is linked to an enzyme substrate which is labeled (referred to as "assay component"). The enzyme is referred to as an "analyte of interest." A composition is formed comprising the enzyme and its labeled substrate, and the composition is incubated to allow the enzyme to cleave the substrate. (Steps (a)(ii) and (b)). Following cleavage, the nanotube is separated from the composition and the label is induced to luminesce. (Steps (c) and (d)). In this assay, the enzyme substrate is not "linked" to the electrode, and Massey does not teach or suggest linking the enzyme substrate to an electrode. Accordingly, Massey does not render claims 55 or 56 obvious.

2. Claim 60

Massey and Shukla also fail to render amended claim 60 obvious. Applicants have amended claim 60 by deleting "capture moiety" and inserting "solid phase, wherein said solid phase is not a graphitic nanotube." Shukla does not teach or suggest the use of a solid phase of any kind. Massey teaches the use of carbon nanotubes as an integral part of the disclosed assays. For example, all the methods disclosed in columns 12-14 of Massey include the formation of a complex comprising a "graphitic nantoube." These graphitic nanotubes can be used as a solid phase onto which substrates are attached, and can be used to bring the ECL-label into proximity to the electrode. As stated by Massey, [t]he general structure of the solid phase was as

follows: fibril-substrate (scissile bond)-$Ru(bpy)_3^{2+}$." Col. 40, lines 18-19. In the method described on column 13, lines 32-57 of Massey, the nanotubes are magnetically charged and are collected on the electrode using a magnetic field. In contrast, the instant specification discloses numerous solid phases such as solids, semi-solids, gels, films, membranes, meshes, felts, composites, particles, and the like. *See* for example page 11, line 28 to page 12, line 3. The specification also discloses carbon nanotubes as a solid phase. See specification, page 14, lines 5-7.

Applicants respectfully submit that *In re Johnson* and *In re Wertheim* make clear that an applicant may exclude any species in a claim disclosed in the specification. *In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A. 1977) and *In re Wertheim*, 191 USPQ 90, 98 (CCPA 1976). According to M.P.E.P. § 2173.05(i),

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.

M.P.E.P. § 2173.05(i) (citation to *In re Johnson* omitted); *see also In re Wertheim.*

Here, carbon nanotubes as a solid phase were disclosed, including on page 14, lines 5-7 of the specification. Accordingly, the amendment of claim 60 is fully supported by the specification, and no new matter has been added by this amendment.

B. There is No Motivation to Combine Shukla and Massey

Shukla provides no motivation to combine its teachings with Massey because no problem was perceived by Shukla. To find a motivation to modify a reference, there must be some deficiency or problem perceived with the prior art reference. *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000) (stating "there was no apparent

disadvantage to the dead-bolt mechanism of Johnson, and therefore the motivation to combine would not stem from the "nature of the problem" facing one of ordinary skill in the art, because no 'problem' was perceived"). Shukla did not perceive deficiencies related to the method of detection.

With respect to the Office's assertion that a desire for enhanced efficiency would motivate the combination of Shukla with Massey, Shukla notes that "the apparent disadvantage in the time-course of the gel assay is more than compensated for by its direct applicability to unfractionated extracts." Shukla, page 1631. Further, the same "apparent disadvantage" of Shukla requiring fractionation with a gel would be present in Massey. In fact, Massey provides no fractionation analogous to the gel of Shukla which permitted application to unfractionated extracts.

With respect to sensitivity, Shukla notes that "the inability to detect particular DNA helicases was expected based on the characteristics of these enzymes in the standard helicase assay." *Id.* Shukla notes that "these limitations in the sensitivity of the activity gel assay can be overcome easily by substituting the appropriate substrates." *Id.* In particular, Shukla notes that "[t]he DnaB and the PriA DNA helicases could not be detected in the activity gel assay in part because they required a particular structure or sequence that was not in the activity gel DNA substrate." *Id.* Similarly, Shukla notes that DNA helicase III was not detected because it migrated to a region of the gel that was heavily populated with nuclease activities and that a 2-dimensional activity gel could eliminate this problem. *Id.* Massey provides no method to eliminate this problem. The problems noted by Shukla involve incompatibility with the enzymes or their substrates, not with detection per se. Because Shukla does not teach or suggest

that the shortcomings of Shukla would be addressed through changing the detection mechanism there is no motivation to combine the gel assay of Shukla with the electrochemiluminescent binding assay of Massey. Moreover, as noted above, Shukla and Massey do not teach that an ECL label could easily be substituted for the radioactivity used in Shukla. The skilled artisan, when provided with Shukla's sensitive assay for detecting enzymes using radioactivity would not be motivated to develop an ECL-based assay that might involve extensive experimentation to develop a method for detecting an ECL-labeled substrate that is affixed to a membrane.

In view of these remarks, Applicants respectfully request that the Office withdraw the rejection of claims 55-64, 67, 69, and 85-87.

VI. New Claims

Applicants provide new claims 90 and 91. These claims correspond to cancelled claims 48 and 49, which have been re-written in independent form with the incorporation of the limitations of the claims from which they previously depended (claim 46). These claims recite two different methods in which multiple enzyme reactions can be measured simultaneously. The ability to measure multiple enzyme activities simultaneously is described in the specification:

> "Substrates can be immobilized on different regions of one or more solid phases to form a patterned array of substrates. Such a patterned array having two or more regions comprising substrates that differ in structure from each other could be used to simultaneously measure the activity of two or more enzymes (the substrates are chosen for their known specificity for a particular enzyme of interest)," and "[a]lternatively, the substrates can be patterned on an array of independent electrodes so that labels in a particular region can be selectively induced to emit ECL by the

> selective application of voltage to selected electrodes. In this alternative embodiment, imaging is not necessary."

Specification, page 14, line 22 to page 15, line 5.

For example, in one embodiment, a sample contains an enzyme that joins substrates A and B, and a second enzyme joins substrates C and D. In an embodiment encompassed by claim 90, substrates A and C, are the first substrates of the first and second enzymes, respectively, and are linked to a label. Substrates B and D and are the second substrates of the first and second enzymes, respectively, and are linked to an electrode in a patterned array. This configuration would allow for the measurement of the first enzyme activity (joining A and B) and the second enzyme activity (joining C and D), by measuring the light produced along the length of the electrode, with substrates B and D located on different places on the electrode so that the signals can be distinguished. Of course, there can be many more substrate pairs that could be measured simultaneously by using additional locations on the electrode.

Claim 91 is similar to claim 90. However, in an embodiment encompassed by claim 91, rather than linking the different second substrates (e.g. B and D in the discussion above) to different regions of an electrode, the second substrates the linked to distinct electrodes. Therefore, substrate B is linked to a different electrode than substrate D. The enzyme activity that joins A and B and the activity that joins C and D can be measured by monitoring the light produced from the different electrodes. Voltage could be applied simultaneously or at different times to the electrodes and light emission visualized with a camera or other light detection device capable to identifying the source of the light. As in claim 90, claim 91 is not limited to measuring the activity of

two enzymes, but can be used to measure more than two enzyme activities at the same time.

Applicants also provide new claims 92 and 93, which recite methods by which multiple cleavage reactions can be measured simultaneously. These claims correspond to cancelled claims 58 and 59, which have been re-written in independent form with the incorporation of the limitations of the claim from which they previously depended (claim 56). They are similar to new claims 90 and 91 and reflect embodiments in which substrates are linked to the same electrode in a patterned array, or in which the substrates are linked to independent electrodes that form a patterned array.

VII. Conclusion

In view of the foregoing remarks, Applicant submits that the claimed invention, as amended, is not obvious in view the publications of record and that the claims are in form for allowance. Should the Examiner wish to discuss this application, the Examiner is encouraged to contact the undersigned at the number below.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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